Paper for submission to: Industrial Engineering Chemistry Research

Draft: 5th November 2013

The solvation and dissociation of 4-benzylaniline hydrochloride in chlorobenzene

Emma K. Gibson [1], John M. Winfield [1], David Adam [1], Alice A. Miller [2], Robert H. Carr [3], Archie Eaglesham [3] and David Lennon * [1].

1. School of Chemistry, Joseph Black Building, University of Glasgow, Glasgow, UK G12 8QQ.
2. School of Computing Science, Sir Alwyn Williams Building, University of Glasgow, Glasgow, UK G12 8QQ.
3. Huntsman (Europe) BVBA, Everslaan 45, 3078 Everberg, Belgium.

Corresponding author
Dr David Lennon,
School of Chemistry,
Joseph Black Building,
University of Glasgow,
Glasgow G12 8QQ, U.K.

E-mail: David.Lennon@glasgow.ac.uk;
Tel: (+44) (0)-141-330-4372

Abstract

A reaction scheme is proposed to account for the liberation of 4-benzylaniline from 4-benzylaniline hydrochloride using chlorobenzene as a solvent and at a temperature of 373 K. Two operational regimes are explored: 'closed' reaction conditions correspond to the retention of evolved hydrogen chloride gas within the reaction medium, whereas an 'open' system permits gaseous hydrogen chloride to be released from the reaction medium. The solution phase chemistry is analysed by ^{1}H NMR spectroscopy. Complete liberation of solvated 4-benzylaniline from solid 4-benzylaniline hydrochloride is possible under 'open' conditions, with the entropically favoured conversion of solvated hydrogen chloride to the gaseous phase thought to be the thermodynamic driver that effectively controls a series of interconnecting equilibria. A kinetic model is proposed to account for the observations of the open system.

Keywords: 4-benzylaniline, 4-benzylaniline hydrochloride, process intensification, kinetic model.

1. Introduction

Polyurethanes have wide application in society, being used in such diverse areas as the automobile, furnishing and surface coating industries.[1] They may be prepared from isocyanates, which are typically obtained by the phosgenation of aromatic amines in the presence of chlorobenzene as a solvent.[1] In this case, a carbamoyl chloride is formed initially, which subsequently decomposes to form the desired isocyanate, Equations 1 and 2. However, hydrogen chloride is released at each stage and undergoes a side reaction with aromatic amine starting material to form an unwanted hydrochloride salt, Equation (3).

$$RNH_2 + COCl_2 \rightarrow RNHC(O)Cl + HCl \quad (1)$$

$$RNHC(O)Cl \rightarrow RNCO + HCl \quad (2)$$

$$RNH_2 + HCl \rightarrow RNH_3Cl \quad (3).$$

The amine hydrochloride precipitate is highly insoluble in the reaction medium and, unless treated, could lead to a significant yield loss within the process. However, the precipitate reacts slowly and endothermically with phosgene to produce the desired isocyanate, Equation 4..[1,2]

$$RNH_3Cl + COCl_2 \rightarrow RNCO + 3HCl \quad (4).$$

The processing of the amine hydrochloride precipitate constitutes a resource intensive process,[1,2] so an improved understanding of the decomposition of the hydrochloride salt (the back reaction of equation 3) is appropriate and could lead to improvements in the efficiency of the isocyanate production process; this issue is examined in the present work.

Previous work by Gibson *et al* has reported on the structural and spectroscopic characteristics associated with the hydrochlorination of 4-benzylaniline [3] and 4,4′-methylenedianiline [4] in chlorobenzene. Badawi has recently analysed the structure and vibrational spectra of 4,4′-methylenedianiline.[5] The work of Gibson *et al* showed the dissolution of hydrogen chloride

gas in chlorobenzene required rigorous mixing and, even then, it was only sparingly soluble.[3] This communication is concerned with liberating 4-benzylaniline (4-BA, $C_6H_5CH_2C_6H_4NH_2$), a model compound with chemical functionality representative of reagents used in certain isocyanate production chains,[3] from 4-benzylaniline hydrochloride (4-BA.HCl, $C_6H_5CH_2C_6H_4NH_3^+Cl^-$), Equation 5.

$$4-BA \bullet HCl_{(s)} \xrightarrow{\text{chlorobenzene}} 4-BA_{(solv)} + HCl_{(solv)} \quad (5),$$

where the subscripts (s) and (solv) signify solid and solvated species respectively. Reflecting the industrial operation,[1] chlorobenzene is used as the solvent.

Despite the relevance of Equation 5 to the operation of large-scale production facilities, there is a paucity of literature on the factors influencing liberation of the aromatic amine in a representative process solvent. Liberation of starting material (4-BA) from by-product (4-BA.HCl) might be achievable by varying the reactor configuration during dissolution experiments. Scheme 1 presents a three-stage reaction scheme as one possibility. Firstly, solid 4-BA.HCl is solvated (4-BA.$HCl_{(solv)}$), secondly 4-BA.$HCl_{(solv)}$ dissociates to form solvated 4-BA and hydrogen chloride (4-$BA_{(solv)}$ and $HCl_{(solv)}$) then, finally, the solvated hydrogen chloride partitions in to the gaseous phase. This article examines the feasibility of Scheme 1 and considers the effect of laboratory reactor configurations that facilitate either (i) the retention of HCl within the reaction environment (this constitutes a ‘closed’ system) or (ii) the release of gaseous HCl from the reaction environment (this constitutes an ‘open’ system). A kinetic model is proposed to account for the trends observed experimentally with the open reaction system. Moreover, these actions lead to an improved understanding of a pathway within the complexity of industrial scale phosgenation process chemistry.

Scheme 1 hereabouts

<u>Scheme 1</u>. A possible reaction scheme for the dissolution of solid 4-BA.HCl in chlorobenzene. K_1 is the equilibrium constant corresponding to the solvation of 4BA.HCl from solid 4-BA.HCl, with k_1 and k_{-1} the associated forward and backward rate coefficients. K_2 is the equilibrium constant corresponding to the dissociation of solvated 4BA.HCl, with k_2 and k_{-2} the associated forward and backward rate coefficients. K_3 is the equilibrium constant corresponding to the partitioning of solvated HCl into the vapour phase, with k_3 and k_{-3} the associated forward and backward rate coefficients.

Our interest in the behaviour of HCl coincides with the development of high specification Deacon catalysts, that facilitate the inter-conversion of HCl in to Cl_2.[6] In principle, chlorine so-produced could be exploited to produce phosgene, thereby helping to close the chlorine cycle.[7]

2. Experimental

Samples of solid 4-benzylaniline hydrochloride, 4-BA.$HCl_{(s)}$, were prepared and characterized by ^{1}H NMR and FTIR spectroscopy as described previously.[3] M.p. = 453 K, consistent with a previous report [3] and thermal gravimetric analysis showed negligible mass loss below 403 K. Thus, in order to maximise 4-BA.HCl solubility whilst avoiding the possibility of thermal decomposition of the starting material, dissolution measurements in chlorobenzene (b.p. = 415 K) were performed at 373 K. Numerical fitting routines were configured within the Origin graphical software package (OriginLab Corporation, Version 7.5). The reference compound 4-benzylaniline (Alfa-Aesar, purity 98%) was used as received; m.p. = 313 K.

2.1 Dissolution studies

Reactions were performed within a fume cupboard using a Radley's Carousel 6 reaction station (Radley's Discovery Technologies) with 25 cm^3 flasks and a head space above solution of 75 cm^3. The carousel housed 6 reaction vessels, each treated to identical mixing (baffled flasks and cross-shaped stirrer bars) and temperature conditions. Each reactor was connected to a condenser unit. Continuous mixing was maintained at all times at a rate so as to sustain a vortex in the liquid phase that facilitated vigorous exchange between the gas/liquid and solid/liquid interfaces.

Two reactor configurations were adopted. Firstly, for operation in a 'closed' configuration, the reactor was sealed and liquid samples were extracted for analysis by means of a syringe sampling through a PTFE septum. This arrangement prevented gaseous hydrogen chloride from leaving the reaction environment, *i.e.* liquid plus headspace. Secondly, for an 'open' configuration the septum was simply removed from the top of the reactor, so that any gaseous hydrogen chloride would be irreversibly exspelled from the reaction medium.

Chlorobenzene (15 cm^3, Aldrich, purity 99.8 %, < 0.005 % water) with 4-BA.HCl in each of the six carousel flasks was maintained at 373 K for periods up to 25 h. For the closed series of experiments approximately 0.03g of 4-BA.HCl was used (9.10 mmol dm^{-3}); for the open experiments approximately 0.02 g of 4-BA.HCl was used (6.07 mmol dm^{-3}). Liquid samples taken by syringe were filtered using Whatman inorganic Anotop syringe filters (0.2μm porosity) before NMR analysis. Blank measurements where a thermocouple was placed in each flask confirmed the reaction temperature was maintained at 373 K throughout the duration of the solubilisation experiments.

2.2 Quantitative ^{1}H NMR spectroscopy

^{1}H NMR spectra were recoded using a Bruker Avance 400 MHz spectrometer. The solubility of 4-BA in chlorobenzene at 298 K is 4.722 (± 0.034) mol dm^{-3}, whereas the solubility of 4-BA.HCl in chlorobenzene at 293 K is 0.26 (± 0.13) mmol dm^{-3} and rises to 0.52 (± 0.19) mmol dm^{-3} at 333 K.[3] A conventional single pulse ^{1}H NMR spectrum collected using 8000 scans over an 8 h period afforded a detection limit of only 0.1 mmol dm^{-3}; insufficient to analyse 4-BA.HCl$_{(solv)}$. Thus, in order to improve sensitivity, a solvent suppression pulse program [8,9] was deployed to suppress the otherwise dominant chlorobenzene resonance. Pre-saturation of chlorobenzene resonances at 6.939 and 7.092 ppm was achieved using a power level of 60 db and a pulse length of 3 s. These arrangements afforded a ten-fold enhancement in detection limit in a 30 minute acquisition time, albeit with some loss of signal stability .

Quantification was achieved by fitting an NMR glass capillary containing a measured quantity of dichloromethane in C_6D_6 into the NMR sample tube. The use of deuterated benzene as a solvent for the internal reference avoided any spectral overlap in the 2 - 6 ppm region of the spectrum where the diagnostic methylene and amine resonances are located. The use of the glass insert ensured no interaction between the deuterated solvent and the reference material with the reaction mixture. Spectroscopic measurements undertaken using a variety of pulse lengths and delays between successive pulses confirmed relaxation effects were not perturbing spectral intensity.[8,9] Experiments were performed at least in duplicate, with the datasets presented here being representative of all measurements.

Blank experiments were performed using solutions of 4-BA at concentrations comparable to the saturation limit of 4-BA.HCl. Occasionally, one of a set of six measurements would display a minor discontinuity in intensity, attributed to instabilities in the phase matching of

the solvent suppression program.[9] Peak intensities were determined by integration of the relevant spectral features. Resonances of the -CH_2- and -NH_2 groups appeared at 3.76 and ≈ 3.0 ppm respectively. The latter resonance was relatively broad, indicating a degree of exchange with protonic material. Infrared spectroscopy has shown the presence of a small number of water molecules to be inherently present in the chlorobenzene solvent;[3] thus, it is assumed that exchange between these highly dispersed water molecules and the amine groups of 4-$BA_{(solv)}$ is responsible for the broadening of the amine resonance. For the open system measurements, all of the solid 4-BA.HCl was solvated for times exceeding *ca*. 10 h and the integrated -CH_2- and -NH_2 resonances were normalized to a plateau value that corresponded to the original 4-BA.HCl concentration (6.00 ± 0.10 mmol dm^{-3}). This scaling of a single dataset enabled a correction for the variance in the absolute intensities obtained when applying the solvent suppression pulse sequence between different experimental runs.

3. Results

3.1 The Closed System

Figure 1 shows the ^{1}H NMR spectrum of 4BA.$HCl_{(s)}$ in chlorobenzene at 373 K as a function of time and shows a sequential growth in intensity of the CH_2 resonance at 3.76 ppm. No signal due to a NH_2 resonance at ≈ 3 ppm [3] is observed in any of the spectra. Calibration measurements using the integrated intensity of the methylene resonance of 4-BA indicate the spectral acquisition conditions used here yield a detection limit 0.01 mmol dm^{-3}. From Scheme 1, the CH_2 resonance could correspond to the combined concentration of 4-$BA_{(solv)}$ and 4-BA.$HCl_{(solv)}$, whereas the NH_2 resonance represents solely 4-$BA_{(solv)}$. It is assumed therefore that the CH_2 signal represents exclusively 4-BA.$HCl_{(solv)}$ for the spectra presented in Figure 1.

Figure 1 herebouts

<u>Figure 1</u>. Solution phase ^{1}H NMR spectra of a mixture of 4-BA.HCl(s) and chlorobenzene as a function of time at 373 K in a stirred and sealed reactor. The CH_2 resonance is observed at 3.76 ppm. The times displayed on each spectrum represent the sampling times of the reaction after commencement of reaction. Signals at 3.26 and 4.26 ppm are due to impurities in the reaction medium.

Calibration of the NMR spectra presented in Figure 1 leads to the concentration profile displayed in Figure 2. Associating the CH_2 signal solely to 4-BA.HCl$_{(solv)}$, the concentration increases quite rapidly in the first 5 h, thereafter it rises more slowly, approaching a saturation value *ca*. 2.25 mmol dm^{-3} after 24 h. The data are well described by an exponential growth function, Equation 6.[10]

$$\left[4-\mathrm{BA}\bullet\mathrm{HCl}_{(\mathrm{solv})}\right]_t=\left[4-\mathrm{BA}\bullet\mathrm{HCl}_{(\mathrm{solv})}\right]_\infty\left(1-e^{-k_1t}\right) \qquad (6),$$

where [4-BA.HCl$_{(solv)}$]$_t$ and [4-BA.HCl$_{(solv)}$]$_\infty$ are respectively the concentration of 4-BA.HCl$_{(solv)}$ at time t and at saturation, and k_1 is the rate coefficient for the dissolution process, as described in Scheme 1.

Figure 2 hereabouts

<u>Figure 2.</u> Concentrations associated with the CH_2 ^{1}H NMR signals for a mixture of 4-BA.HCl(s) and chlorobenzene at 373 K as a function of time in a stirred and sealed reactor. The solid line represents a least squares fit of the CH_2 resonance to a first order exponential growth function, Equation 6.

The solid line in Figure 2 represents a least squares fit of the CH_2 resonance data to Equation 6, with the evident goodness of fit suggesting that the 4-BA.HCl dissolution process conforms

to first order kinetics. It might be expected that the dissolution of 4-BA.HCl$_{(s)}$ would follow zero order kinetics, as is often encountered in, for instance, drug release systems.[11] However, one reason for this outcome could be the limited solubility of the hydrochloride salt in the process solvent.[3]

Equation 6 can be redefined in terms of expressing 4-BA.HCl$_{(solv)}$ as the product, Equation 7.

$$\ln\left(1-\frac{\left[4-\mathrm{BA}\bullet\mathrm{HCl}_{(\mathrm{solv})}\right]_{\infty}}{\left[4-\mathrm{BA}\bullet\mathrm{HCl}_{(\mathrm{solv})}\right]_{t}}\right)=-k_1 t \qquad (7).$$

Figure 3 shows a plot of the first order integrated rate equation for product formation for four separate runs. With the exception of a single data point, the dataset is well correlated to a linear fit, consistent with a 1st order process; k_1 = 2.4 (± 0.3) x 10^{-3} min^{-1} and [4-BA.HCl$_{(solv)}$]∞ = 1.87 (± 0.53) mmol dm^{-3}. The errors correspond to 1 standard deviation in the determination of the mean rate coefficient and salt saturation value from the four separate runs. It is noted that non-dissolved 4-BA.HCl$_{(s)}$ was present at the end of all four reactions as evidenced by the presence of solid particles in the solution. The saturation limit observed here is higher than reported previously at a broadly comparable temperature [0.52 (± 0.19) mmol dm^{-3} at 333 K].[3] However, the original measurements were made using a different vessel, indicating some sensitivity of 4-BA.HCl solubility to temperature, reactor configuration and possibly residual water.

Figure 3 hereabouts

<u>Figure 3</u>. First order product plot for 4-BA.HCl$_{(solv)}$ as a function of time at 373 K in chlorobenzene under closed conditions. Four experimental datasets are presented, designated A – D. The straight line represents the optimum fit for all of the data points.

The data presented above may be used to estimate the equilibrium constant associated with the dissociation of 4-BA.$HCl_{(solv)}$, K_2 (Scheme 1). Equation 8 represents a definition of K_2.

$$K_2 = \frac{\left[4-\mathrm{BA}_{(\mathrm{solv})}\right]\left[\mathrm{HCl}_{(\mathrm{solv})}\right]}{\left[4-\mathrm{BA.HCl}_{(\mathrm{solv})}\right]} \qquad (8).$$

Assuming $[4BA_{(solv)}] \leq 0.01$ mmol dm^{-3}, $[HCl_{(solv)}]$ must also be ≤ 0.01 mmol dm^{-3}. Given that 4-BA.HCl saturates at 1.87 mmol dm^{-3}, then from Equation 8, $K_2 < 5.35 \times 10^{-8}$ mol dm^{-3}. It is concluded that closed conditions do not favour the efficient liberation of 4-BA.

3.2 The Open system

In the open configuration, septa at the top of each of the six reactors were removed, so that any gaseous material, specifically HCl (Scheme 1), released in to the headspace above the solution phase was vented to atmosphere. A mixture of 4-BA.HCl was combined with chlorobenzene (corresponding to a concentration of 6.07 mmol dm^{-3}), maintained at 373 K under conditions of continuous stirring, as described in Section 2.1, and analysed by ^{1}H nmr spectroscopy as a function of time. The concentration values corresponding to the resulting CH_2 and NH_2 resonances are presented in Figure 4.

Figure 4(a) shows the profile for the CH_2 resonance to be significantly different to that observed in a closed system (Figure 2). Up to approximately 7 h time the growth of intensity of the methylene resonance is linear, consistent with zero order kinetics, thereafter it plateaus at *ca*. 6 mmol dm^{-3}. Further, in marked contrast to the closed system, Figure 4(b) shows the NH_2 resonance to be evident; displaying an almost sigmoid-like dependence on time: For a period of up to *ca*. 6 h the concentration of $4BA_{(solv)}$ increases quite slowly then abruptly rises to maximum intensity at *ca*. 6 mmol dm^{-3}, where it too plateaus.

Figure 4 hereabouts

<u>Figure 4.</u> (a) Concentrations associated with the CH_2 ^{1}H NMR signals for a mixture of 4-BA.HCl(s) and chlorobenzene at 373 K as a function of time in a stirred and open reactor. The solid line represents a linear fit to the CH_2 resonance in the time period 0-7 h and the dashed line indicates a plateau concentration value at extended times. (b) Concentrations associated with the NH_2 ^{1}H NMR signals for a mixture of 4-BA.HCl(s) and chlorobenzene at 373 K as a function of time in a stirred and open reactor. The triangles signify the concentration of 4-BA.HCl$_{(solv)}$ calculated according to Equation 12. The solid line represents a fit of the calculated [4-BA.HCl$_{(solv)}$] concentration in the time period 6-23 h to a first order exponential decay as signified by Equation 13. The error bars represent 1 standard deviation of the mean from four replicate measurements of standard solutions.

The NH_2 resonance signifies the presence of 4-BA. When both the CH_2 and NH_2 resonances are observed, as is the case with Figure 4, then the presence of the CH_2 resonance corresponds to a contribution from 4-BA.HCl$_{(solv)}$ and 4-BA$_{(solv)}$. Therefore, in an open system, the concentration associated with the $\delta(CH_2)$ signal at any time t, $[\delta(CH_2)]_t$, and the associated concentration of the $\delta(NH_2)$ signal, $[\delta(NH_2)]_t$, are respectively given by Equations 9 and 10.

$$\left[\delta(\mathrm{CH_2})\right]_t = \left\lfloor 4-\mathrm{BA}\bullet\mathrm{HCl}_{(solv)}\right\rfloor_t + \left\lfloor 4-\mathrm{BA}_{(solv)}\right\rfloor_t \qquad (9).$$

$$\left[\delta(\mathrm{NH_2})\right]_t = \left\lfloor 4-\mathrm{BA}_{(solv)}\right\rfloor_t \qquad (10).$$

Thus, the concentration of solvated 4-BA.HCl at any time t, [4-BA.HCl$_{(solv)}$]$_t$, is given by Equations 11 and 12.

$$\left[\delta(\mathrm{CH_2})\right]_t - \left[\delta(\mathrm{NH_2})\right]_t = \left\{\left\lfloor 4-\mathrm{BA}\bullet\mathrm{HCl}_{(solv)}\right\rfloor_t + \left\lfloor 4-\mathrm{BA}_{(solv)}\right\rfloor_t\right\} - \left\lfloor 4-\mathrm{BA}_{(solv)}\right\rfloor_t \qquad (11).$$

$$\left[\delta(\mathrm{CH_2})\right]_t - \left[\delta(\mathrm{NH_2})\right]_t = \left\lfloor 4-\mathrm{BA}\bullet\mathrm{HCl}_{(solv)}\right\rfloor_t \qquad (12)$$

Application of Equation 12 leads to the values of 4-BA.HCl$_{(solv)}$ presented in Figure 4(b) as triangles. Here, the 4-BA.HCl$_{(solv)}$ content increases to a maximum of *ca*. 3.5 mmol dm^{-3}, then progressively declines to zero concentration. The solid line in Figure 4(b) is a fit of a single exponential decay, as defined by Equation 13, for the data in the period 6 – 24 h.

$$\left[4-\mathrm{BA}\bullet\mathrm{HCl}_{(\mathrm{solv})}\right]_t = \left[4-\mathrm{BA}\bullet\mathrm{HCl}_{(\mathrm{solv})}\right]_{\max} e^{-k_2 t} \qquad (13),$$

where [4-BA.HCl$_{(solv)}$]$_{max}$ is the maximum concentration of 4-BA.HCl$_{(solv)}$ at mixing time, t′, and k_2 is the rate coefficient for the dissociation process, as described in Scheme 1. From Figure 4(b), [4-BA.HCl$_{(solv)}$]$_{max}$ = 3.43 (± 0.52) mmol dm^{-3} at t′ = 6.08 h. The error in [4-BA.HCl$_{(solv)}$]$_{max}$ represents 1 standard deviation from four replicate concentration measurements of standard solutions of 4-BA. The profile of the calculated 4-BA.HCl$_{(solv)}$ data is well described by the fit to Equation 13, indicating that the dissociation process, Equation 14, is consistent with a first order decay process.

$$4-\mathrm{BA}\bullet\mathrm{HCl}_{(\mathrm{solv})} \rightarrow 4-\mathrm{BA}_{(\mathrm{solv})} + \mathrm{HCl}_{(\mathrm{solv})} \qquad (14).$$

The trends evident in Figure 4 may be rationalized with reference to Scheme 1. The initial dissolution stage, K_1, requires a break up of the 4-BA.HCl lattice. The dissociation stage, K_2, involves breaking apart the tight ion pair of the solvated hydrochloride salt. The last stage, K_3, is entropically driven, with the transition from solvated to gaseous HCl representing a large increase in entropy. The fact that 4-BA has a high solubility in chlorobenzene [3] means that if re-dissolution of HCl (k_{-3}) is disfavoured, then significant quantities of the hydrochloride salt can be processed in the manner indicated in Scheme 1 and observed in Figure 4.

The difference between Figure 2 and Figure 4 is attributed to the partitioning of HCl into the vapour phase and subsequent removal from the system in an open configuration. Anhydrous HCl is sparingly soluble in chlorobenzene [1,3,12] but in a closed system there will be a fixed

concentration of $HCl_{(solv)}$ that will constrain equilibrium K_2 (Scheme 1). Thus, as evidenced in Figure 2, a closed system permits only a minor dissolution of the hydrochloride salt. In the open system employed here, HCl that partitions into the vapour phase is extracted from the system. Under these conditions, the dissolution rate is independent of time and exhibits zero order kinetics.

The data points at 23 h in Figure 4 are less intense than that implied by the trend line for the CH_2 resonance at $t \geq 10$ h. As considered in the Experimental section (Section 2.2), single point fluctuation in intensity was periodically observed upon application of the solvent suppression pulse sequence. A replicate run (not shown) exhibited constant CH_2 and NH_2 resonance intensities for $t \geq 10$ h, confirming complete dissolution of $4BA.HCl_{(s)}$ in the 10-24 h period.

4. Kinetic analysis

4.1 Development of a kinetic model

Although the kinetics for consecutive reactions displaying first order kinetics are well described,[10] the situation for consecutive mixed order reactions is less well documented. An exception is the work of Ball, who has derived expressions for a first order first stage process followed by a zero order process.[13] However, to the best knowledge of the authors, no complete derivation is readily available for a consecutive process that proceeds via zero order kinetics but is then followed by a first order process. Consequently, a model is presented herein.

Let the concentrations of $4\text{-}BA.HCl_{(s)}$, $4\text{-}BA.HCl_{(solv)}$ and $4\text{-}BA_{(solv)}$ at time t be respectively signified by the letters A, B and C. Further, a condition is set such that the concentration of A

= 0 and B = B_{max} at time t'. After time, t', the concentration of B follows a first order decay profile.

The consecutive reaction scheme is given by Equation 15:

$$A \underset{\text{zero order}}{\overset{k_1}{\rightarrow}} B \underset{\text{first order}}{\overset{k_2}{\rightarrow}} C \qquad (15).$$

From the zero order part of Equation 15, the following expression holds: $dA/dt = -k_1$. Integrating and applying the initial condition ($A = A_0$ *at* $t = 0$) we get

$$A = -k_1 t + A_0 \qquad (16)$$

until $A = 0$. If t' is the value of t when $A = 0$, $t' = A_0 / k_1$.

The rate of formation of *B* until $t = t'$ is a competition between its formation from *A* and its decay to form *C*. When t ≤ t′, $dB/dt = k_1 - k_2 B$. This first order differential equation is solved using integrating factor $e^{k_2 t}$.[14] The general solution is $Be^{k_2 t} - (k_1/k_2)e^{k_2 t} = c_1$, where c_1 is a constant. Applying the initial condition ($B = 0$ *at* $t = 0$) we have the following solution:

$$B = \frac{k_1}{k_2}\left(1 - e^{-k_2 t}\right) \quad \text{when} \quad t \le t' \qquad (17).$$

When $t \geq t'$, the rate of decay of *B* is dependent only on the transition $B \rightarrow C$. Thus, $dB/dt = -k_2 B$. This ordinary differential equation has the solution $B = c_2 e^{-k_2 t}$, where c_2 is a constant.

Now, from the previous case (Equation 17), we know that at t ≤ t′, $B = k_1\left(1 - e^{-k_2 t}\right)/k_2$. Hence $c_2 = \frac{k_1}{k_2}\left(e^{k_2 t'} - 1\right)$ and

$$B = \frac{k_1}{k_2}\left(\left(e^{k_2 t'} - 1\right)e^{-k_2 t}\right) \quad \text{when} \quad t \geq t' \tag{18}$$

Consider product *C* from Equation 15: $dC/dt = k_2 B$ and it follows from Equations 17 and 18 that $dC/dt = k_1\left(1 - e^{-k_2 t}\right)$ when $t \leq t'$, and $dC/dt = k_1\left(e^{k_2 t'} - 1\right)e^{-k_2 t}$ if $t \geq t'$.

When $t \leq t'$, $dC/dt = k_1\left(1 - e^{-k_2 t}\right)$. Integrating and applying the initial condition (*C = 0 at t = 0*) gives:

$$C = \frac{k_1}{k_2}\left(tk_2 + e^{-k_2 t} - 1\right) \quad \text{when} \quad t \leq t' \tag{19}$$

When $t \geq t'$, $dC/dt = k_1\left(e^{k_2 t} - 1\right)e^{-k_2 t}$, so $C = \frac{-k_1}{k_2}\left(e^{-k_2 t}\left(e^{k_2 t'} - 1\right)\right) + c_3$, for constant c_3. By Equation 19, $C = \frac{k_1}{k_2}\left(t'k_2 + e^{-k_2 t'} - 1\right)$ at t = t′, and it follows that $c_3 = t'k_1$. Hence,

$$C = \frac{k_1}{k_2}\left(\left(e^{-k_2 t}\right)\left(1 - e^{k_2 t'}\right) + t'k_2\right) \quad \text{when} \quad t \geq t' \tag{20}.$$

4.2 Application of kinetic model

Using the solutions for the differential equations for this consecutive reaction sequence, Equations 16 - 20, a non-linear least squares analysis was employed to find k_1 and k_2 and fitted to the experimental concentrations obtained from the NMR resonances, Figure 5. The turning point, t', is the time when the concentration of A is zero and B is at a maximum concentration. Thus, from Figure 4, t' = 6.08 h.

Figure 5 hereabouts

Figure 5 **Concentrations associated with the CH_2 and NH_2 ^1H NMR signals for a mixture of 4-BA.HCl(s) and chlorobenzene at 373 K as a function of time in a stirred and open reactor. The concentrations associated with the CH_2 and NH_2 resonances are indicated by squares and circles respectively. The error bars represent 1 standard deviation about the mean from four replicate measurements of standard solutions of 4-BA. The solid black line represents a fit of the calculated 4-BA(solv) concentration according to Equations (19) and (20). The dashed line represents the summation of 4-BA.HCl(solv) and 4-BA(solv), with the former quantity calculated via Equations (17) and (18).**

The NH_2 concentrations represent experimentally obtained concentrations of 4-$BA_{(solv)}$. The black line is the non-linear least squares fit of Equations 19 and 20 to these data points, providing values for parameters k_1 and k_2, Table 1. The values for the two rate coefficients can then be substituted into Equations 17 and 18 in order to calculate the concentration profile for 4-$BA.HCl_{(solv)}$ over the full reaction coordinate. Adding this predicted concentration profile for 4-$BA.HCl_{(solv)}$ to the calculated value of NH_2 concentrations (Figure 5), the CH_2 concentrations can be predicted via Equation 9. This quantity is plotted in Figure 5 as a dashed line and displays reasonable correspondence to the experimental dataset. Overall, Figure 5 shows the agreement between the predicted values for $[4\text{-}BA.HCl_{(solv)} + 4\text{-}BA_{(solv)}]_t$, as signified by the CH_2 resonance, and $[4\text{-}BA_{(solv)}]_t$, as signified by the NH_2 resonance, to be reasonable.

Table 1 hereabouts

Table 1. **Rate coefficients defined according to Scheme 1 and obtained from a non-linear least square fit of Equations (19) and (20) to the concentration of 4-$BA_{(solv)}$**

determined for a mixture of 4-BA.HCl(s) and chlorobenzene at 373 K as a function of time in a stirred and open reactor (Figure 5). The errors presented signify the range in k values from duplicate experiments.

The kinetic parameters presented in Table 1 are specific to the experimental arrangement employed. In order to optimize solubility values whilst avoiding thermal decomposition limits, as defined by the thermal gravimetric measurements outlined in Section 2, the consistency of the calculated kinetic and equilibrium constants as a function of temperature have not been examined. Further, determination of the sensitivity of the kinetic parameters as a function of mixing conditions was deemed to be beyond the scope of the present investigation. Nevertheless, for the adopted experimental arrangements, the proposed model for the open system plus the derived rate coefficients provide a comprehensive description for a 4-BA liberation process as defined by Scheme 1.

The rate coefficients presented in Table 1 were combined with Equations 16 - 20 to determine the following parameters for the open reaction system over the full reaction coordinate: (i) the consumption of 4-BA.$HCl_{(s)}$ [Equation 16], (ii) the formation/consumption of the intermediate 4-BA.$HCl_{(solv)}$ [Equations 17 and 18] and (iii) the formation of 4-$BA_{(solv)}$ [Equations 19 and 20] The resulting concentration profiles are presented in Figure 6. The point values for 4-BA.$HCl_{(solv)}$ calculated from Equation 12 are also included in the figure and display a fair correspondence to the 4-BA.$HCl_{(solv)}$ profile. Figure 6 represents a comprehensive description of how a well-mixed open system can be employed to liberate 4-$BA_{(solv)}$ from 4-BA.$HCl_{(s)}$.

Figure 6 hereabouts

Figure 6 **Concentrations associated with the NH_2 ^1H NMR signals (circles) for a mixture of 4-BA.HCl(s) and chlorobenzene at 373 K as a function of time in a stirred and open reactor. The rate coefficients from Table 1 have been combined with Equations (16) – (20) to determine (a) the consumption of 4-BA.$HCl_{(s)}$ (dashed black line), (b) the concentration of 4-BA.$HCl_{(solv)}$ (solid grey line) and (c) the formation of 4-$BA_{(solv)}$ (solid black line). The point concentrations of 4-BA.$HCl_{(solv)}$ were calculated by application of equation (12) and are indicated by triangles. The error bars for [4-$BA_{(solv)}$] represent 1 standard deviation about the mean from four replicate measurements of standard solutions. The error bar shown for [4-BA.$HCl_{(solv)}$] corresponds to the range of concentration of B_{max} determined for a duplicate set of measurements.**

5. Discussion

Primarily because of their role in pharmaceutical science, there is a general interest in the solubility of hydrochloride salts and their dissociation in various solvents.[15,16] Further, the solubility of aniline hydrochloride in protic solvents has been studied because of links to the manufacture of anhydrous magnesium chloride, which has application as a precursor for the production of magnesium metal produced by electrochemical methods.[17] However, despite the substantial resource requirement associated with the work-up of the amine hydrochloride precipitate in certain large-scale isocyanate production units (Equation 4),[1] little information is available in the open literature on the solubilisation of relevant amine hydrochloride salts in representative process solvents such as chlorobenzene.[3,4] The present work examines this issue and shows the solubilisation profile of a hydrochloride salt of a model aromatic amine to be sensitive to the form of the reaction environment. For identical conditions of temperature and agitation rate, Scheme 2 illustrates the dramatic contrast between the profile observed

when a closed reactor configuration is used (Scheme 2(a) and Figure 2) compared with an open reactor configuration (Scheme 2(b) and Figure 6).

Scheme 2 hereabouts

Scheme 2. Reaction schemes applicable to (a) closed and (b) open reaction systems.

As noted above, it is assumed that the driving force for Scheme 2(b) is the entropically favoured formation of gaseous hydrogen chloride. Tentatively, it is presumed that this process results in a free energy change sufficient to overcome the favourable enthalpic term associated with the tight ion pair of the solvated hydrochloride salt. In the absence of this free energy change, the limited solubility of 4BA.HCl in chlorobenzene prevents the liberation of 4-BA, as witnessed in a closed reactor configuration.

6. Conclusions

A reaction scheme has been proposed from this laboratory study for the liberation of 4-BA from 4-BA.$HCl_{(s)}$ in chlorobenzene at 373 K. Solution phase ^{1}H NMR spectroscopy is used to analyse the composition of the liquid phase as a function of time. The main results may be summarized as follows.

- In a closed reaction configuration, where evolved HCl from the dissociation of dissolved 4-BA.HCl is retained within the reactor headspace, the dissolution kinetics are shown to be first order. 4-BA.$HCl_{(solv)}$ saturates at 1.87 (± 0.53) mmol dm^{-3}, with a rate coefficient, k_1, of 2.4 (± 0.3) x 10^{-3} min^{-1}. No 4-$BA_{(solv)}$ forms under these conditions.
- In a open reaction configuration, where evolved HCl originating from the dissociation of dissolved 4-BA.HCl is vented from the reactor headspace, there is complete

dissolution of 4-BA.$HCl_{(s)}$ to form 4-$BA_{(solv)}$. The dissolution process exhibits zero order kinetics. Analysis of the ^{1}H NMR signals indicates 4-BA.$HCl_{(solv)}$ to be an intermediate species within a two-stage consecutive process; with the second stage exhibiting first order kinetics. The overall process is entropically driven, via the partitioning of HCl in to the gaseous phase from a solvated state.

- A kinetic model is derived for a two-stage consecutive process with the first stage exhibiting zero order kinetics and the second stage exhibiting first order kinetics. The model is applied to concentration measurements recorded from the open system and provides a good overall fit to the data. Rate coefficients for the first and second stages are respectively determined to be 1.60 ($\pm$ 0.3) x 10^{-2} mmol dm^{-3} min^{-1} and 3.30 ($\pm$ 0.7) x 10^{-3} min^{-1}.
- The model for the open system is used to determine the following three parameters throughout the full reaction coordinate: (i) the consumption of 4-BA.$HCl_{(s)}$, (ii) the formation of the intermediate 4-BA.$HCl_{(solv)}$ and (iii) the formation of 4-$BA_{(solv)}$.

Acknowledgements

Huntsman Polyurethanes are thanked for the provision of postgraduate studentship (EKG). David Rycroft and Jim Gall (University of Glasgow) are thanked for assistance with the NMR measurements. Stewart Parker (STFC ISIS Facility) provided assistance with ancillary vibrational calculations of 4-BA.$HCl_{(s)}$ and 4-$BA_{(s)}$ that helped identify barriers to solvation.

References

(1) Randall, D; Lee, S *The Polyurethanes Book*, John Wiley: Chichester, (2002).

(2) Ulrich, H. *Chemistry & Technology of Isocyanates*, John Wiley: Chichester, (1996).

(3) Gibson, E.K.; Winfield, J.M.; Muir, K.W.; Carr, R.H.; Eaglesham, A; Gavezzotti, A; Parker, S.F.; Lennon, D. A structural and spectroscopic investigation of the hydrochlorination of 4-benzylaniline: the interaction of anhydrous hydrogen chloride with chlorobenzene. *Phys. Chem. Chem. Phys.*, **2009**, *11*, 288-297.

(4) Gibson, E.K.; Winfield, J.M.; Muir, K.W.; Carr, R.H.; Eaglesham, A; Gavezzotti, A; Lennon, D. A structural and spectroscopic investigation of the hydrochlorination of 4,4'-methylenedianiline. *Phys. Chem. Chem. Phys.*, **2010**, *12*, 3824-3833.

(5) Badawi, H. A comparative study of the structure and vibrational spectra of diphenylmethane, the carcinogen 4,4-methylenedianiline and 4,4-methylenebis(N,N-dimethylaniline). *Spectrochim. Acta A*, **2013**, *109*, 213-220.

(6) Over, H; Schomäcker, R. What Makes a Good Catalyst for the Deacon Process? *ACS Catal*. **2013**, *3*, 1034-1046.

(7) Cavani, F. Catalytic selective oxidation: The forefront in the challenge for a more sustainable chemical industry. *Catal. Today*, **2010**, *157*, 8-15.

(8) Freeman, R; *A Handbook of Nuclear Magnetic Resonance*, Longman: Harlow (1987).

(9) Guéron, M; Plateau, P; Decorps, M. Solvent signal suppression in NMR. *Prog. NMR Spect.*, **1991**, *23*, 135-209.

(10) Frost A.A.; Pearson, R.G. *Kinetics and Mechanism*, John Wiley: New York (1961).

(11) Khairuzzaman, A; Ahmed, S.U.; Savva, M.; Patel, N.K. Zero-order release of aspirin, theophylline and atenolol in water from novel methylcellulose glutarate matrix tablets. *Int. J. Pharm.*, **2006**, *318*, 15-21.

(12) Fogg, P.G.T.; Gerrard, W *Solubility of Gases in Liquids : A Critical Evaluation of Gas/Liquid Systems in Theory and Practice*, John Wiley, Chichester, (1991).

(13) Ball, D.W. Kinetics of consecutive reactions: First reaction, first-order; second reaction, zeroth-order. *J. Chem. Educ*. **1998**, *75*, 917-919.

(14) Tebutt, P, *Basic Mathematics for Chemists*, John Wiley: New York (1998).

(15) A.T.M. Serajuddin and C.I. Jarowski, Effect of diffusion layer pH and solubility on the dissolution rate of pharmaceutical bases and their hydrochloride salts I: Phenazopyridine, *J. Pharm. Sci*., **1985**, *74*, 142-147.

(16) A.A. Silkov, Conductometric determination of anilinium ion dissociation constants at various temperatures, *Russ. J. Phys. Chem*., **1999**, *73*, 1224-1228.

(17) S. Sun and Z. Li, Experimental Measurement and Modeling of Aniline Hydrochloride Solubility in Water, Methanol, Ethanol, Propan-1-ol, and Their Mixed Systems, *J. Chem. Eng. Data*, **2012**, *57*, 219–226.

Table

Rate coefficients
$k_1 = 1.60 (\pm 0.3) \times 10^{-2}$ mmol dm^{-3} min^{-1}
$k_2 = 3.30 (\pm 0.7) \times 10^{-3}$ min^{-1}

Table 1. Rate coefficients defined according to Scheme 1 and obtained from a non-linear least square fit of Equations (19) and (20) to the concentration of 4-$BA_{(solv)}$ determined for a mixture of 4-BA.HCl(s) and chlorobenzene at 373 K as a function of time in a stirred and open reactor (Figure 5). The errors presented signify the range in k values from duplicate experiments.

Scheme and Figure captions.

Scheme 1. A possible reaction scheme for the dissolution of solid 4-BA.HCl in chlorobenzene. K_1 is the equilibrium constant corresponding to the solvation of 4BA.HCl from solid 4-BA.HCl, with k_1 and k_{-1} the associated forward and backward rate coefficients. K_2 is the equilibrium constant corresponding to the dissociation of solvated 4BA.HCl, with k_2 and k_{-2} the associated forward and backward rate coefficients. K_3 is the equilibrium constant corresponding to the partitioning of solvated HCl into the vapour phase, with k_3 and k_{-3} the associated forward and backward rate coefficients.

Scheme 2. Reaction schemes applicable to (a) closed and (b) open reaction systems.

Figure 1. Solution phase ^{1}H NMR spectra of a mixture of 4-BA.HCl(s) and chlorobenzene as a function of time at 373 K in a stirred and sealed reactor. The CH_2 resonance is observed at 3.76 ppm. The times displayed on each spectrum represent the sampling times of the reaction after commencement of reaction. Signals at 3.26 and 4.26 ppm are due to impurities in the reaction medium.

Figure 2. Concentrations associated with the CH_2 ^{1}H NMR signals for a mixture of 4-BA.HCl(s) and chlorobenzene at 373 K as a function of time in a stirred and sealed reactor. The solid line represents a least squares fit of the CH_2 resonance to a first order exponential growth function, Equation 6.

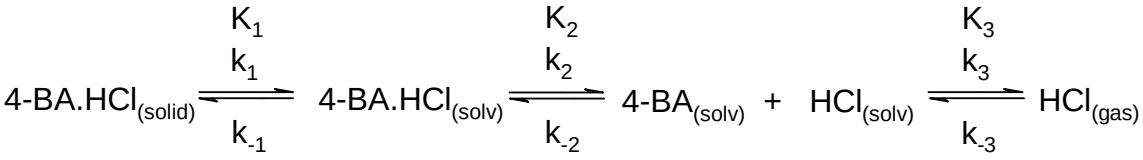
Figure 3. First order product plot for 4-BA.$HCl_{(solv)}$ as a function of time at 373 K in chlorobenzene under closed conditions. Four experimental datasets are presented, designated A – D. The straight line represents the optimum fit for all of the data points.

Figure 4. (a) Concentrations associated with the CH_2 ^1H NMR signals for a mixture of 4-BA.HCl(s) and chlorobenzene at 373 K as a function of time in a stirred and open reactor. The solid line represents a linear fit to the CH_2 resonance in the time period 0-7 h and the dashed line indicates a plateau concentration value at extended times. (b) Concentrations associated with the NH_2 ^1H NMR signals for a mixture of 4-BA.HCl(s) and chlorobenzene at 373 K as a function of time in a stirred and open reactor. The triangles signify the concentration of 4-BA.$HCl_{(solv)}$ calculated according to Equation 12. The solid line represents a fit of the calculated [4-BA.$HCl_{(solv)}$] concentration in the time period 6-23 h to a first order exponential decay as signified by Equation 13. The error bars represent 1 standard deviation of the mean from four replicate measurements of standard solutions.

Figure 5 Concentrations associated with the CH_2 and NH_2 ^1H NMR signals for a mixture of 4-BA.HCl(s) and chlorobenzene at 373 K as a function of time in a stirred and open reactor. The concentrations associated with the CH_2 and NH_2 resonances are indicated by squares and circles respectively. The error bars represent 1 standard deviation about the mean from four replicate measurements of standard solutions of 4-BA. The solid black line represents a fit of the calculated 4-BA(solv) concentration according to Equations (19) and (20). The dashed line represents the summation of 4-BA.HCl(solv) and 4-BA(solv), with the former quantity calculated via Equations (17) and (18).

Figure 6 Concentrations associated with the NH_2 ^1H NMR signals (circles) for a mixture of 4-BA.HCl(s) and chlorobenzene at 373 K as a function of time in a stirred and open reactor. The rate coefficients from Table 1 have been combined with Equations (16) – (20) to determine (a) the consumption of 4-BA.$HCl_{(s)}$ (dashed black line), (b) the concentration of 4-BA.$HCl_{(solv)}$ (solid grey line) and (c) the formation of 4-$BA_{(solv)}$ (solid black line). The point concentrations of 4-BA.$HCl_{(solv)}$ were calculated by application of equation (12) and are indicated by triangles. The error bars for [4-$BA_{(solv)}$] represent 1 standard deviation about the mean from four replicate measurements of standard solutions. The error bar shown for [4-BA.$HCl_{(solv)}$] corresponds to the range of concentration of B_{max} determined for a duplicate set of measurements.

Schemes and Figures



Scheme 1. A possible reaction scheme for the dissolution of solid 4-BA.HCl in chlorobenzene. K_1 is the equilibrium constant corresponding to the solvation of 4BA.HCl from solid 4-BA.HCl, with k_1 and k_{-1} the associated forward and backward rate coefficients. K_2 is the equilibrium constant corresponding to the dissociation of solvated 4BA.HCl, with k_2 and k_{-2} the associated forward and backward rate coefficients. K_3 is the equilibrium constant corresponding to the partitioning of solvated HCl into the vapour phase, with k_3 and k_{-3} the associated forward and backward rate coefficients.

(a). Closed reaction system

$$\text{4-BA.HCl}_{(s)} \overset{K_1}{\rightleftharpoons} \text{4-BA.HCl}_{(solv)}$$

(a). Open reaction system

$$\text{4-BA.HCl}_{(s)} \overset{K_1}{\rightleftharpoons} \text{4-BA.HCl}_{(solv)} \overset{K_2}{\rightleftharpoons} \text{4BA}_{(solv)} + \text{HCl}_{(solv)} \overset{K_3}{\rightleftharpoons} \text{HCl}_{(g)}$$

Scheme 2. Reaction schemes applicable to (a) closed and (b) open reaction systems.

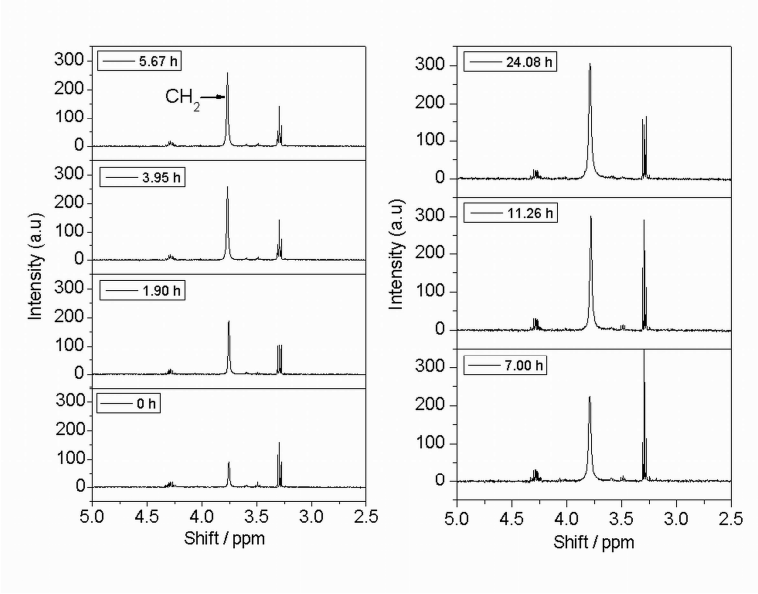


Figure 1. Solution phase ^{1}H NMR spectra of a mixture of 4-BA.HCl(s) and chlorobenzene as a function of time at 373 K in a stirred and sealed reactor. The CH_2 resonance is observed at 3.76 ppm. The times displayed on each spectrum represent the sampling times of the reaction after commencement of reaction. Signals at 3.26 and 4.26 ppm are due to impurities in the reaction medium.

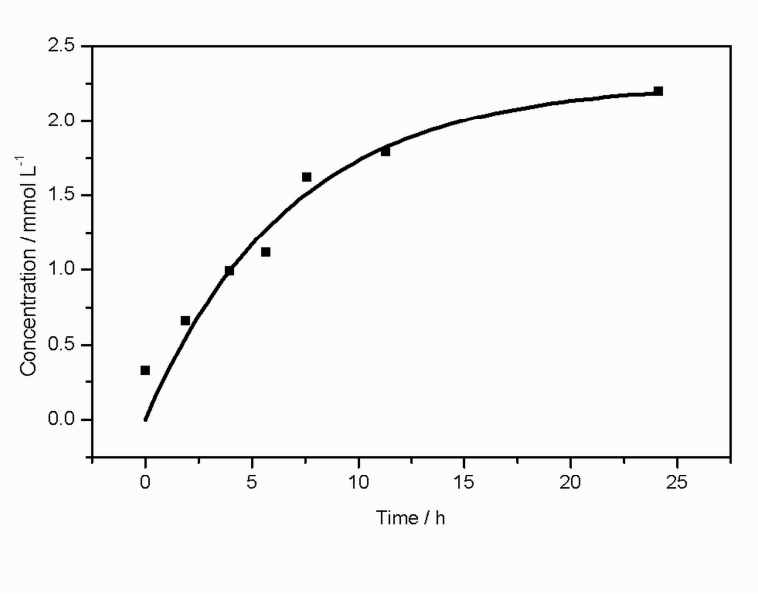


Figure 2. Concentrations associated with the CH_2 ^1H NMR signals for a mixture of 4-BA.HCl(s) and chlorobenzene at 373 K as a function of time in a stirred and sealed reactor. The solid line represents a least squares fit of the CH_2 resonance to a first order exponential growth function, Equation 6.

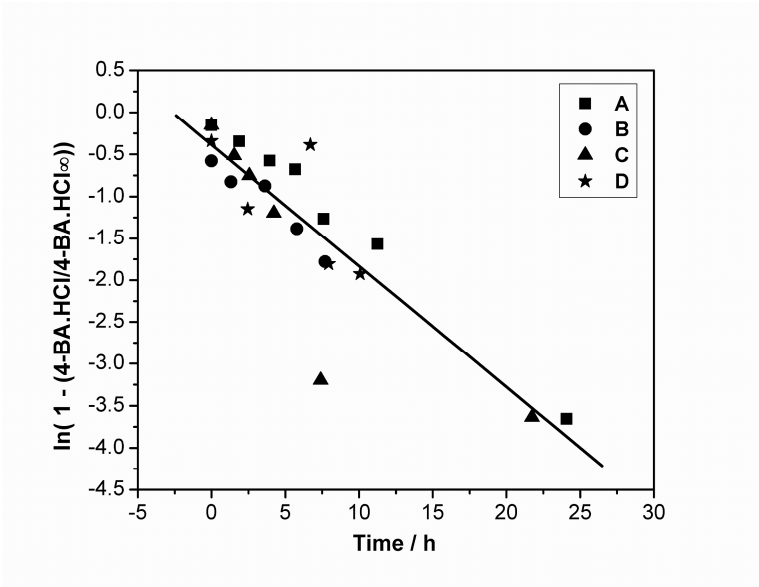


Figure 3. First order product plot for 4-BA.HCl$_{(solv)}$ as a function of time at 373 K in chlorobenzene under closed conditions. Four experimental datasets are presented, designated A – D. The straight line represents the optimum fit for all of the data points.

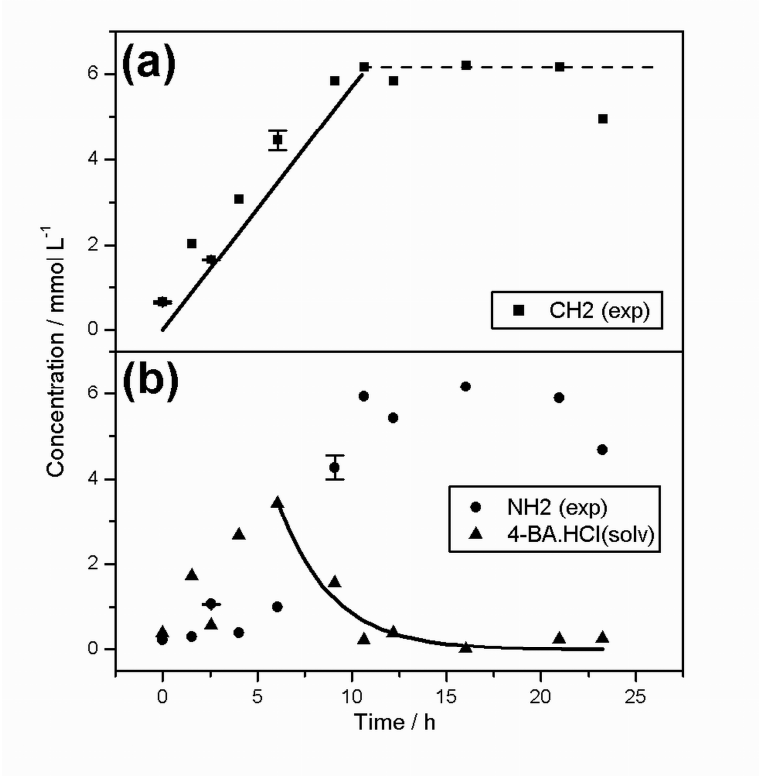


Figure 4. (a) Concentrations associated with the CH_2 ^1H NMR signals for a mixture of 4-BA.HCl(s) and chlorobenzene at 373 K as a function of time in a stirred and open reactor. The solid line represents a linear fit to the CH_2 resonance in the time period 0-7 h and the dashed line indicates a plateau concentration value at extended times. (b) Concentrations associated with the NH_2 ^1H NMR signals for a mixture of 4-BA.HCl(s) and chlorobenzene at 373 K as a function of time in a stirred and open reactor. The triangles signify the concentration of 4-BA.$HCl_{(solv)}$ calculated according to Equation 12. The solid line represents a fit of the calculated [4-BA.$HCl_{(solv)}$] concentration in the time period 6-23 h to a first order exponential decay as signified by Equation 13. The error bars represent 1 standard deviation of the mean from four replicate measurements of standard solutions.

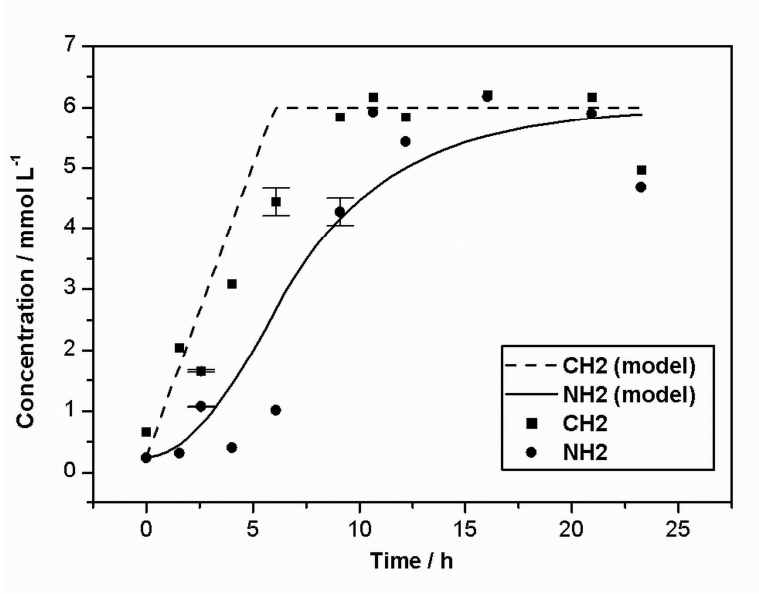


Figure 5 Concentrations associated with the CH_2 and NH_2 ^1H NMR signals for a mixture of 4-BA.HCl(s) and chlorobenzene at 373 K as a function of time in a stirred and open reactor. The concentrations associated with the CH_2 and NH_2 resonances are indicated by squares and circles respectively. The error bars represent 1 standard deviation about the mean from four replicate measurements of standard solutions of 4-BA. The solid black line represents a fit of the calculated 4-BA(solv) concentration according to Equations (19) and (20). The dashed line represents the summation of 4-BA.HCl(solv) and 4-BA(solv), with the former quantity calculated via Equations (17) and (18).

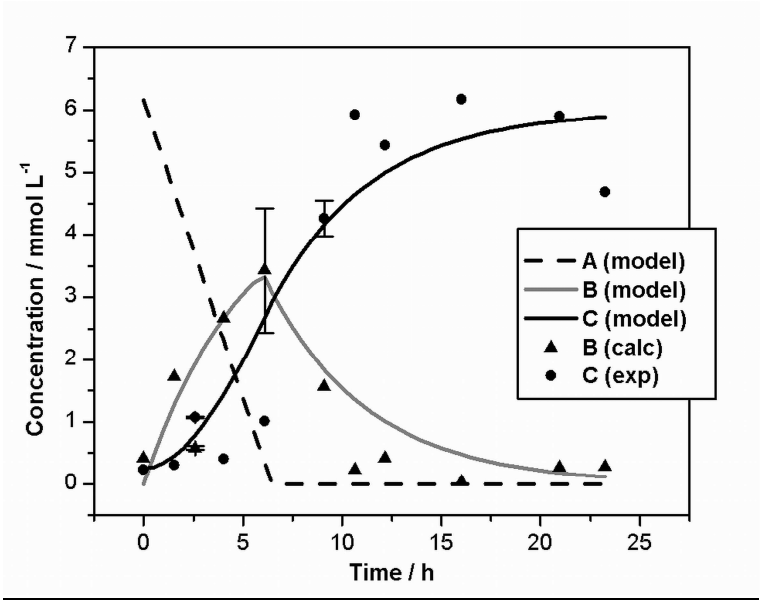


Figure 6 Concentrations associated with the NH_2 ^1H NMR signals (circles) for a mixture of 4-BA.HCl(s) and chlorobenzene at 373 K as a function of time in a stirred and open reactor. The rate coefficients from Table 1 have been combined with Equations (16) – (20) to determine (a) the consumption of 4-BA.$HCl_{(s)}$ (dashed black line), (b) the concentration of 4-BA.$HCl_{(solv)}$ (solid grey line) and (c) the formation of 4-$BA_{(solv)}$ (solid black line). The point concentrations of 4-BA.$HCl_{(solv)}$ were calculated by application of equation (12) and are indicated by triangles. The error bars for [4-$BA_{(solv)}$] represent 1 standard deviation about the mean from four replicate measurements of standard solutions. The error bar shown for [4-BA.$HCl_{(solv)}$] corresponds to the range of concentration of B_{max} determined for a duplicate set of measurements.